immunologic detection, or prevent unwanted endocytosis by cells.

17. The method of claim 15, further comprising the step of chemically modifying at least one of said nanodevice and said microdevice with an organo hydroxyl.

18. (AMENDED) The method of claim 17, further comprising the step of selecting said organo hydroxyl group from the group consisting of poly (ethylene glycol), methoxypoly (ethylene glycol).

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19. The method of claim 15, further comprising attaching a lipid anchor to at least one of said nanodevice and said microdevice with an organo hydroxyl.

REMARKS

1. The drawings were objected to in the Office Action due to minor informalities that have been amended as follows:

In Figure 1, the reference sign for nanochip 30 was modified to clearly distinguish it from the lead line and the RBC border.

Feature 24 representing Electronic Spin Resonance (ESR) was disclosed in the Specification for Figure 3, but was not displayed in the drawing. Feature 24 has been added to Figure 3 to show the ESR process.

Reference sign 120 and 130 were shown in Figure 3 but were not explicitly disclosed in the Specification. No change is being made to Figure 3, but the Specification is amended to explicitly disclose reference signs 120 and 130.

2. The Specification was objected to in the Office Action due to minor informalities that are addressed as follows:

In the middle of paragraph 8, the NMR technique is disclosed as a means of monitoring electron dense nanoparticles. The Office Action states appropriate technology is ESR. Applicant believes that NMR or ESR techniques would be applicable to the monitoring of electrodense particles and has incorporated ESR into the specification in addition to NMR.

The reference to Table 1 in the Specification included a typographical error that was corrected.

3. The Office Action objected to claim 5 due to informality in lack of proper spacing in "methodof". The spacing was corrected to "method of".

Applicants respectfully traverse the Office Action provisional rejection of claims 1-19 under the doctrine of obvious-type double patenting as being unpatentable over claims 1-17 of copending Application No. 09727749. The Office Action asserts the claims are not patentably distinct from one another because the broader claims of this application, which teach a nanodevice circulating in the body or located intra-or extracellularly, anticipate the more specific invention of a nanodevice to monitor a bodily condition disclosed in Application No. 09727749. Applicants respectfully submit that the method for insertion of nano and microdevices into a bodily fluid stream is a separate and distinct invention from the methods of detection body conditions using nano and microdevices. Applicants point out that the techniques associated with entry of these devices into bodily fluid streams or cells employ entirely different technologies than those associated with the detection techniques once in the body. Furthermore, while one would expect that the devices are being inserted into the body for a purpose, a

generalized expectation of medical detection does not obviate the specific detection means disclosed in Application No. 09727749. Applicants respectfully request that the provisional double patenting rejection of claims 1-19 be withdrawn.

4. Various claims were rejected under 35 U.S.C 112.

Claim 4 was rejected for insufficient antecedent basis. Applicant has amended claim 4 to for limitations "the substrate" and "said cell" by reciting proper antecedent basis.

Claims 5, 7, and 8 were rejected for reciting the limitation "said biological member" with insufficient antecedent basis. Applicants have amended claims 5, 7, and 8 by reciting proper antecedent basis.

Claims 3, 5, 6, 8, 9, 11, 14, and 16-19 were rejected as being vague and indefinite for failing to positively set forth a further step in method as to claims 1 and 15. Applicant has modified claims 3, 5, 6, 8, 9, 11 and 14 to state a further step in method. It is respectfully requested that claims 16-19 were in proper form in that they did set forth a further method step.

Claim 10 was rejected as vague and indefinite in setting forth a limitation directed to a method of making rather than a method of using as set forth in claim 1. Applicants deleted claim 10.

Claims 12 and 16 were rejected as vague and indefinite as to how the device is to be "adapted for/to." Applicants amend claims 12 and 16 to be specific as to actions taken within the method step.

Claim 13 was rejected for lack of antecedent basis in claim 1. Applicants amend claim 13 from having dependence on claim 1 to dependence on claim 12 to provide appropriate antecedent basis.

5. Claims 1, 2, 6, 7, and 15 were rejected under 35 U.S.C. 102(b) as being anticipated by Merkle. [Advances in Anti-Aging Medicine, Vol. 1, 277-286, Ed. Ronald M. Katz, Liebert Press, 1996] Applicants respectfully traverse the Office's position that Merkle anticipates claims 1, 2, 6, 7, and 15. See M.P.E.P. §2101.1. Merkle provides no enabling disclosures but merely makes suppositions as to what may be possible sometime in the future. Merkle acknowledges the current state of medical art " Today's surgical tools are, ... large and crude." [Abstract ¶1 Sentence 2] and that the new tools of "Nanotechnology" will be "the manufacturing technology of the 21st century." [Abstract ¶2 Sentence 1] "There is broad agreement (though not consensus) that we will at some point in the future be able to inexpensively fabricate essentially any structure ... ."[Introduction ¶1 Sentence 1] Merkle estimates that if progress continues as expected, "... we should have some form of molecular manufacturing by 2010 or 2020. After this, the medical applications will require some additional time to develop." [Abstract ¶2 Sentence 1] In identifying detailed applications of the new technology, Merkle makes clear that development work is left to others.

In rejecting claims 1, 2, 7, and 15 under 35 U.S.C. 102(b) as being anticipated by Merkle, the examiner cites "Merkle disclosure in section 4, last paragraph, [nano]devices in the circulatory system that (section 5, 2d paragraph) circulate freely throughout the body and able to enter individual cells. This disclosure necessarily includes devices in any or all of the following milieus: blood vessels, interstitial spaces (extracellular) and intercellular." Examination of Section 5, 2d paragraph of Merkle reveals that the passage merely compares the size of nanodevices with the size of blood cells (nanodevices being smaller) and observes that nanodevices would be able to enter the circulatory system and individual cells. Merkle, however, fails to enable one of ordinary skill in the art to arrive at the claimed invention without undue experimentation. Section 4, last paragraph simply observes that "The device would

circulate freely throughout the body ... ." No where does Merkle teach how device insertion into the bloodstream or any other area of the body would be achieved. As such, Merkle is a not an enabling disclosure with respect to claims 1, 2, 6, and 7. Furthermore, in Section 6 ¶2 of the Office Action, it is acknowledged that "Merkle does not teach methods of inserting into a cell."

In rejecting claim 6 under 35 U.S.C. 102(b) as being anticipated by Merkle, the Office states "Merkle discloses in section 5, [nano] device with a small computer able to determine the concentration of specific molecules, and able to receive broadcast instructions. These attributes necessarily include the limitation in the invention disclosed in claim 6." Applicants maintain, however, that this is a simple suppositive statement without any enabling disclosure with respect to the microdevices of claim 6.

As the disclosures of Merkle are not enabling and inoperative with respect to claims 1, 2, 6, 7, and 15, Applicants respectfully request that the claims be allowed.

6. Claims 3-5, and 8 were rejected under 35 U.S.C. 103(a) as being unpatentable over Merkle.

As discussed above, Applicant argued that independent claims 1 was not disclosed by Merkle in such a way to enable one of ordinary skill in the art to arrive at the claimed invention without undue experimentation, and therefore should be allowed. As claims 3-5 and 8 are dependent claims based on independent claim 1, they should likewise be allowed.

7. Claims 9-11 and 14 were rejected under 35 U.S.C. 103 (a) as being unpatentable over Merkle in view of Peeters US Patent No. 6123819.

As discussed above, Applicant argued that independent claim 1 was not disclosed by Merkle in such a way to enable one of ordinary skill in the art to arrive at the claimed invention

without undue experimentation, and therefore should be allowed. As claims 9-11 and 14 are dependent claims based on independent claim 1, they should likewise be allowed.

8. Claims 12 and 13 were rejected under 35 U.S.C. 103 (a) as being unpatentable over Merkle in view of Ehnholm US Patent No. 5882304..

As discussed above, Applicant argued that independent claim 1 was not disclosed by Merkle in such a way to enable one of ordinary skill in the art to arrive at the claimed invention without undue experimentation, and therefore should be allowed. As claims 3-5 and 8 are dependent claims based on independent claim 1, they should likewise be allowed.

9. Claims 16-19 were rejected under 35 U.S.C. 103 (a) as being unpatentable over Merkle in view of Schlecter et al. US Patent No. 5071964.

As discussed above, Applicant argued that independent claim 15 was not disclosed by Merkle in such a way to enable one of ordinary skill in the art to arrive at the claimed invention without undue experimentation, and therefore should be allowed. As claims 16-19 are dependent claims based on independent claim 15, they should likewise be allowed.

10. Claim 19 were rejected under 35 U.S.C. 103 (a) as being unpatentable over Merkle in view of Dustin et al. US Patent No. 5071964.

As discussed above, Applicant argued that independent claim 15 was not disclosed by Merkle in such a way to enable one of ordinary skill in the art to arrive at the claimed invention without undue experimentation, and therefore should be allowed. As claims 3-5 and 8 are dependent claims based on independent claim 15, they should likewise be allowed.

Applicant respectfully submits the entire application is now in condition for allowance. Should the Examiner believe that anything further is necessary in order to place the application in condition for allowance, or if the Examiner believes that a personal or telephone interview would be advantageous to resolve the issues presented, he is invited to contact the Applicant's undersigned attorney at the telephone number listed below.

Date: 7-24-2002

Respectfully submitted

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APPENDIX (MARKED-UP SPECIFICATION, CLAIMS AND DRAWINGS)

IN THE SPECIFICATION

Please replace the paragraph bridging pages 4 and 5 with the following paragraph:

Referring now to Figure 1, a nanodevice or microdevice 30 may be operatively attached to red blood cell 20 in one embodiment. The normal, mature discoid human red blood cell 20 has a mean diameter A of approximately 8 μm, a mean cell thickness B (comprising rim and central thickness) of approximately 1.7 μm, a single cell volume of approximately 95 fl, and a surface area of approximately 135 sq. μm. <u>C represents the width of a center of a red blood cell.</u> Typical capillary sizes are approximately 3-4 μm and typical splenic sinusoids are approximately 1 μm. Therefore, a microdevice or nanodevice of 100 nm may be accommodated within the volume of a normal human red blood cell 20 (mean diameter of approximately 8 μm or the red blood cells of other animal species with a mean diameter of approximately 5-10 μm). Intracellular inclusion of the nanodevice or microdevice 30 should not adversely affect red blood cell structure or function, but will vastly extend the circulation time of the nanochip. For example, human red blood cells circulate for 120 days while murine (mouse) cells survive for 50 days. In contrast, unmodified extracellular nanodevices or microdevices free within the blood stream would likely have survival times of minutes to hours due to mechanisms such as phagocytosis or other immunological reactions.

Replace the last paragraph on page 7 with the following paragraph:

A technology that is applicable for nanodevice sensory detection is Electron Spin Resonance (ESR) or Electron Paramagnetic Resonance (EPR). Referring now to Figure 3, EPR 24 is the process of resonant absorption of microwave radiation by paramagnetic ions or molecules, with

at least one unpaired electron spin, and in the presence of a static magnetic field. Figure 3 illustrates EPR 24 detection method with nanodevice 130 within a cell 120. EPR can be used to detect free radicals, odd electron molecules, transition metal complexes, lanthanade ions, and triplet state molecules in vivo. Some examples of detectable materials include phosphorus, arsenic, sulphur, germanium, and organic free radicals such as Di-phenyl-b-picryl-hydrazyl (DPPH). Detectable spin probes based on nitroxide free radicals can be used to detect biological activity such as oxidant stress and pH levels. Concentrations of spin probes can be used to enhance the sensitivity of EPR technology.

Replace the 1st paragraph starting on page 8 with the following paragraph:

Referring now to Figures 4-6, another technology applicable for nanodevice sensory detection is a nanotuning fork detection method. Figure 4 illustrates the nanotuning fork detection method with an intracellular nanodevice 230. Figure 5 illustrates the nanotuning fork detection method with an extracellular membrane 36 bound nanodevice 330. Figure 6 illustrates the nanotuning fork detection method with a fluid phase nanodevice 430. The nanotuning fork can be either unmodified or modified with poly(ethylene glycol) or its derivatives. Referring now to Figure 7, electron dense nanoparticles or nanodevices 530 with spin probes attached can be used as passive blood flow sensors for determining pathologic changes in tissue blood flow. These nanodevices can be used for in vivo blood flow detection utilizing Nuclear Magnetic Resonance (NMR) or ESR technologies. These nanodevices will allow the measurement of blood flow and the detection of any blockages that may inhibit the flow of blood.

Please replace the paragraph bridging pages 8 and 9 with the following paragraph:

NMR technology places a substance in a strong magnetic field that affects the spin of the atomic nuclei of certain isotopes of common elements. Radio wave frequencies passes through the substance then reorients these nuclei. When the wave is turned off, the nuclei release a pulse of energy that provides data on the molecular structure of the substance and that can be transformed into an image by computer techniques. Typical substances that can be used for NMR spectroscopy and imaging are shown in Table 1.[[i] 1.[i]]

IN THE CLAIMS

3. (AMENDED) The method of claim 2, further comprising the step of inserting at least one of said microdevice and said nanodevice into a cell. wherein said cell is a red blood cell.

4. (AMENDED) The method of claim [1] 2, wherein the step of inserting further comprises the step of inserting [the] a substrate into said cell via at least one of reversible osmotic lysis, electroporation, microfine needle injection, and particle gun injection.

5. (AMENDED) The [methodof] method of claim 1, further comprising the step of inserting at least one of said microdevice and nanodevice into a biological member, wherein said biological member is selected from the group consisting of a blood cell, lipid molecules, a liver cell, a nerve cell, a skin cell, a bone cell, a lymph cell, an endocrine cell, a circulatory cell, and a muscle cell.

6. (AMENDED) The method of claim 1, wherein the step of providing at least one of said microdevice and said nanodevice further comprises providing at least one of said nanodevice

and said microdevice [is] selected from the group consisting of a diagnostic system, a transmitter, a receiver, a battery, a transistor, a capacitor, and a detector.

7. (AMENDED) The method of claim 1, wherein at least one of said nanodevice and said microdevice is inserted within [said] a biological member.

8. (AMENDED) The method of claim 1, further comprising the step of inserting at least one of said microdevice and nanodevice into a biological member, wherein said biological member is one of a red blood cell and lipid molecules.

9. (AMENDED) The method of claim 1, [wherein] further comprising the step of selecting a substrate for at least one of said nanodevice and said microdevice [has a substrate selected] from the group consisting of Gallium Arsenide, silicon, and silicon oxides.

10. Deleted [The method of claim 1, wherein at least one of said nanodevice and said microdevice is formed using one of optical lithography, electron beam lithography, ion beam lithography, X-ray lithography, and spatial phase-locked electron beam lithography.]

11. (AMENDED) The method of claim 1, wherein the step of providing at least one of said microdevice and said nanodevice, further comprises providing at least one of said nanodevice and said microdevice [is] of a resonance type nanodevice.

12. (AMENDED) The method of claim 1, [wherein] further comprising detecting at least one of

said nanodevice and said microdevice [is adapted for detection] by one of electron paramagnetic resonance (EPR), electron spin resonance (ESR) and nuclear magnetic resonance (NMR).

13. (AMENDED) The method of claim [1] 12, wherein EPR detects molecules selected from the group consisting of free radicals, odd electron molecules, transition metal complexes, lanthanade ions and triplet state molecules.

14. (AMENDED) The method of claim 1, <u>further comprising the step of selecting a material for</u> [wherein] at least one of said nanodevice and said microdevice [includes a material selected] from the group consisting of phosphorus, arsenic, sulfur, germanium and organic free radicals.

16. (AMENDED) The method of claim 15, further comprising the step of chemically modifying at least one of said nanodevice and said microdevice [such that it is adapted] to prolong vascular retention, prevent immunologic detection, or prevent unwanted endocytosis by cells.

18. (AMENDED) The method of claim 17, <u>further comprising the step of selecting</u> [wherein] said organo hydroxyl group [is selected] from the group consisting of poly (ethylene glycol), methoxypoly (ethylene glycol).

19. The method of claim 15, further comprising attaching a lipid anchor to at least one of said nanodevice and said microdevice with an organo hydroxyl.

IN THE DRAWINGS

Please see attached proposed drawing corrections.

XILL-3095

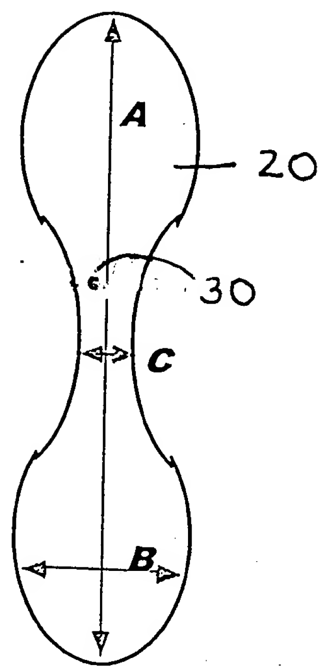

Figure 1

XILL-3095

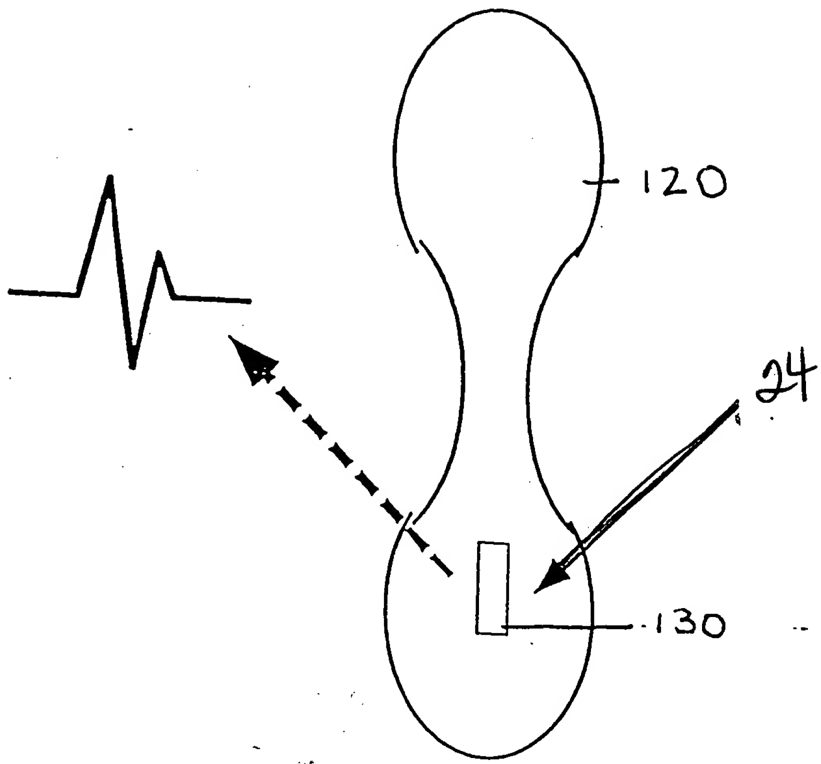

Figure 3